Potential of arbidol for post-exposure prophylaxis of COVID-19 transmission-preliminary report of a retrospective case-control study

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Author Contribution Statement

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Yisheng Zhang, Yanan Li, Yifan Zhou, Wenjing Wang, Yan Wan, Yaling Wang and Ling Mao collected data;
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Abstract

Objective: we postulated that post-exposure prophylaxis (PEP) using Arbidol is associated with decreased infection among individuals exposed to confirmed cases of COVID-19 infection.

Methods: We conducted a retrospective case-control study on family members and health care workers who were exposed to patients confirmed to have SARS-CoV-2 infection by real-time RT-PCR and Chest CT from January 1 to January 16, 2020. We collected demographic information, work location of exposure, post-exposure prophylaxis information, and symptoms, if any, 24 days after exposure. The relation between post-exposure prophylaxis and infection in household contacts and healthcare workers were respectively analyzed.

Results: 27 families and 124 health care workers had evidence of close exposure to patients with confirmed COVID-19. There were no differences in age, profession and sex distribution in the two groups with different post-exposure prophylaxis, table 1. Logistic regression based on the data of the family members and health care workers with Arbidol or Oseltamivir prophylaxis showed that Arbidol PEP was a strong protective factor against the development of COVID-19 (Odds ratio 0·011 , 95% CI 0·001-0·125, P=0·0003 for family members and Odds ratio 0·049, 95%CI 0·003-0·717), P= 0·0276 for health care workers). On the contrary, Oseltamivir was associated with an increase in COVID-19 infection (Odds ratio 20·446, 95% CI 1·407-297·143, P= 0·0271).

Limitations: Limitations of this study include the retrospective design of case-control studies and potential selection bias because the collection of data was through telephone calls.

Conclusions: Our findings suggest Arbidol could reduce the infection risk of the novel coronavirus in hospital and family settings. This treatment should be promoted for PEP use and should be the subject of further investigation.

Key words: Arbidol; COVID-19; SARS-CoV-2; Post-exposure prophylaxis

1. Introduction

Literature and clinical evidence indicate that person-to-person transmission of SARS coronavirus the second (SARS-CoV-2), the pathogen that causes COVID-19, is highly efficient. A sample of 1,099 patients with laboratory-confirmed COVID-19 in China delineates that there were 31·30% had been to Wuhan and 71·80% had contacted with people from Wuhan [1], the source city of the outbreak. The transmission of COVID-19 in families is very efficient; in a report of a family with six members who travelled to Wuhan, five were identified as infected with COVID-19[2].The disease transmission aboard the well-known Diamond Princess cruise ship is potentially a model for understanding the efficiency of SARS-CoV-2 transmission in a dense hospital building inhabited by thousands of patients and health care workers. More than 3600 passengers have been stuck on the cruise ship since February 4 when the primary case was confirmed of COVID-19 on February 1. Following a 14days quarantine period, a total of 624 people tested positive for SARS-CoV-2[3]. Quarantine and post-exposure prophylaxis (PEP) are options to prevent disease transmission. The well-known PEP for influenza infections is Oseltamivir [4], however, there is no such pharmacologic agent demonstrated to prevent COVID-19 transmission after unprotected exposure to infected individuals. Arbidol (Umifenovir) is a broad-spectrum anti-viral agent that is now widely used in China because of its use in treating influenza and recently its potential efficacy in treating COVID-19. Several *in vitro* studies indicate that Arbidol possesses inhibitory effect on coronavirus [5-7] and its derivative, Arbidol mesylate is even stronger against SARS-CoV [7]. One study indicated that the therapeutic index of Arbidol (or selective index) on coronaviridae was 11·8, which is much higher than for orthomyxoviridae, which are 2·4 and 2·5 for influenza A/Aichi/2/68(H3N2) and B/Beijing/184/93, respectively[4]. Clinical trials on the efficacy of Arbidol on COVID-19 are ongoing. Given the increasingly awareness of Arbidol, health care workers and members of the public are turning to Arbidol for both treatment and PEP. We conducted a retrospective case-control study to evaluate the potential efficacy of post-exposure prophylaxis with Arbidol in reducing transmission of SARS-CoV-2.

2. Methodology

2.1 Definition and identification of cases and controls

We analyzed two case-control cohorts: family members and health care workers. In the first cohort, case patients were family members of confirmed cases of COVID-19 who became infected after exposure while controls were family members who were exposed but did not become infected. Each of the 27 families had one primary case of confirmed COVID-19. The families included in the analysis had consulted our hospital regarding PEP and potential treatment options of COVID-19 (Table1).

The second case-control cohort comprised of 124 health care workers in Wuhan Union hospital (WHUH) initially exposed to a cluster of COVID-19 infected colleagues without standard respiratory protection. Cases were workers who became infected and controls were workers who did not become infected. All of the source patients (the primary cases and the cluster of health care workers) were infected between January 1 and January 16, 2020.

2.2 Data Collection

For all case patients and controls, we collected personal demographic information, how and where the primary case was diagnosed, whether or not other family members or the health care workers were on PEP and if so, who in the families were on PEP, the medication used, dosage and duration of treatment, etc. We also inquired for the emergence of fever and/or respiratory symptoms after exposure to the primary case after a duration of 24 days, which is the longest incubation time ever reported for COVID-19[1]. The inquiry was performed through telephone calls. The diagnostic confirmation of COVID-19 was determined by real-time PCR (RT-PCR) on sputum sample or throat swab as described in recent literature [8,9] and the coexistence of viral-like pneumonia on Chest CT.

2.3 Statistical Analysis

We excluded all primary cases in the analysis. *Chi*-square test and logistic regression was applied using R 3·3·0, in which outcome (COVID-19 infected or not infected) was set as the dependent variable; age stratification, gender, time delay until starting PEP, adult or child (for family members), PEP with Arbidol, and PEP with medicine other than Arbidol were set as

independent variables. $P < 0{\cdot}05$ was defined as statistically significant. Missing information was assigned a separate variable of "unknown" and the subjects were not removed from the logistic regression.

3. Results

3.1 General characteristics of cases and controls

We surveyed 27 families who had one primary case of COVID-19 infection and collected data from 66 family members (Table1). 13 family members were cases and 53 were controls (Table 2). Collectively, 45 family members used Arbidol PEP and 1 became infected (Table 3), while 21 family members use Oseltamivir or no PEP and 12 became infected (Table 4). Univariate analysis showed no significant differences in gender (P = 0·09), age (P =0·25) or adult and children distribution between cases and controls (P =0·22) (Table 2).

We analyzed data from 124 health care workers (Table 2), of whom 55 used Arbidol PEP and 1 became infected, while 68 used Oseltamivir and 7 became infected (Table 5). There was no significant difference in gender (P = 0·15), age (P = 0·60), or professional (doctor or nurse) distribution (P = 0·74) between the cases and controls. The cases all worked in the inpatient department (IPD) while the controls were distributed amongst the fever clinic, quarantine ward and inpatient ward. There was no statistically significant difference in work place between the two groups (P = 0·07) (Table 2).

3.2 Logistic Regression

Logistic regressions demonstrated that age stratification, gender, PEP dosage, PEP duration, time from confirmation of suspected case of COVID-19 and starting PEP, and occupation of the health care workers were not statistically significant to the outcome of infection (Table 2). The only significant factor was the medication used for PEP. Arbidol demonstrated a very strong protective factor against COVID-19 infection (Odds ratio 0·011 , 95% CI 0·001-0·125, P=0·0003 in family members and Odds ratio 0·049, 95%CI 0·003-0·717, P= 0·0276 in health care workers) (Table 6) . While in the health care worker cohort, using Oseltamivir for prophylaxis did not work and was associated with increased disease (Odds ratio 20·446, 95% CI 1·407-297·143, P= 0·0271) (Table 7).

3.3 Post-exposure prophylaxis Dosages

There were no differences in dose, the length of days of the medication, delay time of PEP after the diagnosis or primary case in family and health care workers cohorts with or without Arbidol PEP as shown in table 3 and 5. Arbidol PEP dosage used by health care workers was more consistent and all but one used 200mg, Tid, 5-10 days (the one person used 100mg, Tid for 7 days). All persons who chose Oseltamivir PEP used 75mg, Qd.

4. Discussion

Wuhan Union Hospital is the first hospital to recommend compassionate prescription of Arbidol for patients with confirmed or suspected COVID-19 in China. The early release of Therapeutic and Triage Strategy for 2019 Novel Coronavirus in WHUH and the publication of it later on [10] helped health care workers to figure out a possible way for post-exposure prophylaxis and this information was transmitted to some community families directly or indirectly through the health care workers in this hospital.

The low Odds ratios for the family members and the health care workers on Arbidol PEP suggests a very strong protective effect of Arbidol against COVID-19 transmission. On the contrary, Odds ratio for those health care workers on Oseltamivir for PEP is relatively much larger (20·446). Despite this observation, it is hard to conclude that Oseltamivir increases the likelihood of COVID-19 infection. It is possible that work location played a significant role in disease transmission despite not demonstrating statistical significance in our analysis. The neurology department where the cluster of health care worker infections began is located in the internal medicine building, which is home to 800 medical beds. All the health care workers with Arbidol prophylaxis were working in fever clinic and quarantine ward with proper protection, while the workers taking Oseltamivir prophylaxis were working in the inpatient building and the protection protocol was not as strict as those in the areas with high exposure potential. If we take the transmission model in the Diamond Princess cruise ship into consideration 3, a likely explanation

is that all of the infected health care workers had been continuously exposed to a dangerous inpatient ward environment without efficient protection. Additionally, the workers in the fever clinic and quarantine ward may have been more vigilant about taking PEP than their counterparts in the inpatient wards.

Limitations of this study include the retrospective design of case-control studies and potential selection bias because the collection of data was through telephone calls. We did not assess the awareness level of the family members towards Arbidol PEP which may have influenced the decision of some families to choose Oseltamivir instead of Arbidol. The association between Arbidol PEP and prevention of COVID-19 transmission is significant and necessitates a well-designed, large scale, prospective study to further validate the use of Arbidol for post-exposure prophylaxis.

5. Conclusions

Our findings suggest Arbidol could reduce the infection risk of the novel coronavirus in hospital and family settings. This treatment should be promoted for PEP use and should be the subject of further investigation.

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Author Contribution Statement

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Table 1: Evidence of post-exposure prophylaxis potential of Arbidol on COVID-19 transmission in families with household contact

	Primary case*	family members (gender and age in parentheses)	Who on chemoprophylaxis / delay days of post-exposure prophylaxis after the primary case under medial suspicion / ABD chemoprophylaxis, dosage, length /duration of outcome evaluation was 24 days post-exposure
The families received ABD chemoprophylaxis post-exposure to primary case, n=48			
1 Family ZJ [a]	primary case (M, 58)	wife (F,58)	wife / 1 / ABD, 0·2g, Tid, 7 ds / no symptom
2 Family YC [b]	primary case (M, 57)	wife (F,56) and daughter(F,30)	wife and daughter / 4 / ABD, 0·4g, Qd, 5 ds; / no symptom
3 Family ZY [c]	primary case (F, 66)	husband (M,69)	husband / 6 / ABD, 0·2g, Tid, 14 ds / no symptom
4 Family CXL [e]	primary case (F, 30),	husband (M,31)	husband /1/ ABD, 0·2g, Tid, 5 ds / no symptom
5 Family HLB [g]	primary case (F, 27)	wife (F,28)	wife / 1 / ABD, 0·2g, Tid, 10 ds / no symptom
6 Family ZY [g]	primary case (M, 44),	wife (F,39), mother (F, 62), father (M,62), 1 daughter (F, 8), younger brother (M,35), sister-in-law (F,34) and 2 nieces (F,12 and F, 6)	all on post-exposure prophylaxis /8/ ABD, 0·2g, Tid, 8 ds for adult, 0·1g, Tid for children, 8 ds / no symptom for all
7 Family LQH [g]	primary case (F, 54)	husband (M, unclear) and a son (M, unclear)	husband and son / 9 / ABD, 0·2g, Tid, 14 ds / no symptom
8 Family WJ [g]	primary case (M, 40)	wife (F,38), father (M,76), mother (F, unclear) and a son (M,18)	father, mother, wife and son / 6 / ABD, 0·2g, Tid, 4 ds / no symptom
9 Family FJ [g]	primary case (M, 44)	mother (F,69) and an uncle (M, 52)	mother and uncle / 3 / ABD, 0·2g, Tid, 5 ds / all no symptom
10 Family CJP [g]	primary case (F, 40)	mother (F,69), husband (M,40) and 2 kids (unclear, unclear)	mother and husband / 1 /ABD, 0·2g, Tid, 14 ds / husband **confirmed** COVID-19, kids shew no symptom
11 Family JX [e]	primary case (F, unclear)	husband (M,31)	husband /10/ ABD, 0·2g, Tid, 4 ds / no symptom
12 Family FQC [g]	primary case (F, 37)	mother (F,60) and father (M,63)	mother /13/ ABD / 0·2g, Tid, 5 ds / father **confirmed** COVID-19
13 Family WML [g]	primary case (M, 62)	wife (F,45) and 2 kids (gender is unclear,12 and 14)	wife / 2/ 0·2g, Tid, 6ds / all no symptom
14 Family HZY [g]	primary case (F, 68)	daughter (F, 40) and son (M,38)	daughter / 3 / 0·2g, Tid, 4 ds/ son **confirmed** COVID-19
15 Family WCY [g]	primary case (F, 81)	son (M, 41), daughter in low (F,42) and 2 grandchildren (gender is unclear,12 and 16)	son, daughter in low and 2 grandchildren / 9 / ABD, 0·2g, Tid; child aged 12, 0·1g, Tid, 5 ds, / all no symptom
16 Family YM [g]	primary case (F, 67)	husband (M,69), a son (M, 41), a daughter in low (F,39) and a grandson (M,6)	husband, son, and daughter in low / 6 / ABD, 0·2g, Tid, 6 ds / all no symptom
17 Family LZH [e]	primary case (M, 48)	Wife (F, 45)	wife/ 2 / ABD, 0·2g, Tid, 10 ds / no symptom
18 Family LM [f]	primary case (F, 63)	husband(M,65), daughter (F,36) and son in low (M, 37)	husband, daughter and son in low / 1 / 0·2 ABD, Tid, 9 ds / all no symptom
19 Family LM [g]	primary case (F, 42)	husband (M,41) and a daughter (F,12)	husband and daughter / 9/ABD, 0·2g Tid, 5 ds / no symptom
20 Family FXL [g]	primary case (F, 31)	mother (F,68) and husband (M, 32)	mother and husband / 6/ ABD, 0·2g, Tid, 6 ds / no symptom

21 Family CXL [g]	primary case (F, 36)	husband (M,38)	husband /5/ ABD, 0·2g, Tid, 6 ds / no symptom
22 Family ZDH [g]	primary case (M, 34)	wife (F,33)	wife / 11 / ABD, 0·2g, Tid, 5 ds / no symptom
The families did not receive other medicine other than ABD for post-exposure chemoprophylaxis, n=12			
1 Family LID	primary case (F, 66)	husband (M,69)	husband / no chemoprophylaxis / husband **confirmed** of COVID-19
2 Family ZQL [e]	primary case (F, 37)	husband (M,37) and mother (F,67)，grandmother(F, unclear)	mother and husband/ 0/ OSTV, 75mg, Qd, 5 ds / grandmother and husband **confirmed** of COVID-19
3 Family XW [g]	primary case (F, 35)	husband (M,37), mother (F,62), father (M,63) and a daughter (F,6)	Daughter/ 0/ OSTV 75mg Qd, 4 ds / mother and husband **confirmed** of COVID-19
4 Family XY [g]	primary case (F, 33)	husband (M,33) and father (M, 62)	father and husband / 2 / OSTV, 75mg Qd, 5 ds / father and husband **confirmed** of COVID-19
5 Family XM [g]	primary case (F, 38)	husband (M,39), mother (F,65) daughter (F,8) and grandmother(F, unclear)	All did not receive prophylactic medication / grandmother, husband and daughter **confirmed** of COVID-19

***** The primary cases of COVID-19 were confirmed by SARS-CoV-2 RT-PCR positive in throat swab and viral-like pneumonia in chest CT.

[a] Both are clinical doctors, wife taken Arbidol for prophylaxis by husband's advice; the husband is an expert in respiratory and emergency medicine;

[b] A family with no medical knowledge, daughter has inquired treatment strategy on COVID-19 from an expert in respiratory and emergency medicine, taken Arbidol for prophylaxis 0.4 Qd with no doctors' advice;

[c] A family with no medica knowledge, husband has inquired treatment strategy on COVID-19 from an expert in respiratory and emergency medicine;

[d] A family with no medical knowledge, wife exposed same index patient of confirmed COVID-19 as the wife of Family ZY;

[e] Patient is clinical doctors or nurse, inquired treatment strategy from a treatment strategy (ref.).

[f] Wife is clinical doctor, grandmother taken Arbidol by her advice

[g] A family with no medical knowledge, family members inquired treatment strategy from network consulting and doctor friend's advice.

ABD = Arbidol, OSTV = Oseltamivir, F=Female, M=male

Table 2: Demographic data and characteristics of the subjects

	Health care workers (n=124)			Family Members (n=66)		
	Case (n=8)	**Control (n=116)**	***P****	**Case (n=13)**	**Control (n=53)**	***P****
Age (years), mean ± SD	35·1±4·2	34·3±7·7	··	43·4±18·0	39·6±20·6	··
Age stratification	··	··	0·60	··	··	0·25
< 34	4 (50·0)	69 (59·5)	··	2 (15·4)	17 (32·1)	··
≥ 34	4 (50·0)	47 (40·5)	··	9 (69·2)	30 (56·6)	··
Unknown	0 (0·0)	0 (0·0)	··	2 (15·4)	6 (11·3)	··
Adulthood	··	··	··	··	··	0·22
yes	8 (100·0)	116 (100·0)	··	12 (92·3)	41 (77·4)	··
no	0 (0·0)	0 (0·0)	··	1 (7·7)	12 (22·6)	··
Gender, n (%)	··	··	0·15	··	··	0·09
Male	3 (37·5)	20 (17·2)	··	9 (69·2)	20 (37·7)	··
Female	5 (62·5)	96 (82·8)	··	4 (30·8)	27 (50·9)	··
Unknown	0 (0·0)	0 (0·0)	··	0 (0·0)	6 (11·3)	··
Occupation	··	··	0·74	··	··	··
Doctor	3 (37·5)	37 (31·9)	··	0 (0·0)	2 (0·38)	··
Nurse	5 (62·5)	79 (68·1)	··	0 (0·0)	0 (0·0)	··
Others	0 (0·0)	0 (0·0)	··	13 (100·0)	51 (96·2)	··
Working place	··	··	0·07	NA	NA	NA
Fever clinic	0 (0·0)	22 (19·0)	··	NA	NA	NA
IPD¶	8 (100·0)	68 (58·6)	··	NA	NA	NA
Quarantine ward	0 (0·0)	26 (22·4)	··	NA	NA	NA

chi square test;
¶IPD = Inpatient department·
NA=not applicable

Table 3: Arbidol chemophylaxis in the members of community family ¶

	Arbidol (n=45)		
	Case (n=1)	**Controls (n=44)**	***P****
Dose (mg), mean ± SD	600·0 ± 0·0	560·0 ± 0·1	NA
Days with Arbidol, mean ± SD	14·0 ± 0·0	6·9 ± 2·8	NA
Time with Arbidol	··	··	0·24
< 7 days	0 (0·0)	26 (59·1)	··
≥ 7 days	1 (100·0)	18 (40·9)	··
Days to prophylaxis, mean ± SD	1·0 ± 0·0	6·0 ± 3·2	NA
Time of delay	··	··	0·15
< 5 days	1 (100·0)	14 (31·8)	··
≥ 5 days	0 (0·0)	30 (68·2)	··

**Chi* square test;
¶Digits in the parentheses are percentages if not defined·
NA=not applicable

Table 4: Relation between Arbidol prophylaxis and infection in community family

Treatment		Case No. (%)	Control No. (%)	OR (95% CI) *	*P**
Arbidol	NO	12 (92·3)	9 (17·0)	1·00 (Reference)	··
	YES	1 (7·7)	44 (83·0)	0·011 (0·001-0·125)	0·0003

* Logistic regression calculations, gender, age and occupation adjusted
No.= Number

Table 5: Arbidol or Oseltamivir chemophylaxis in health care workers ¶

	Oseltamivir (n=68)			Arbidol (n=55)		
	Case (n=7)	Control (n=61)	*P**	Case (n=1)	Control (n=54)	*P**
Dose (mg), mean ± SD	75·00±0·00	75·00±0·00	NA	0·60±0·00	0·48±0·18	NA
Days with Arbidol or Oseltamivir, mean ± SD	9·67±4·22	10·57±2·28	NA	14·00±0·00	9·13±5·64	NA
Time with Arbidol or Oseltamivir	··	··	0·6671	··	··	0·2333
< 10 days	1 (14·3)	4 (6·6)	··	0 (0·0)	27 (50·0)	··
= 10 days	4 (57·1)	46 (75·4)	··	0 (0·0)	13 (24·1)	··
>10 days	1 (14·3)	11 (18·0)	··	1 (100·0)	13 (24·1)	··
unknown	1 (14·3)	0 (0·0)	··	0 (0·0)	1 (1·9)	··
Days to prophylaxis, mean ± SD	2·60±2·88	3·75±5·39	NA	0·00±0·00	5·75±7·75	NA
Time of delay (days)	··	··	0·1376	··	··	0·4017
= 0 day	2 (28·6)	34 (55·7)	··	1(100·0)	18 (33·3)	··
1-5 days	2 (28·6)	6 (9·8)	··	0 (0·0)	13 (24·1)	··
> 5 days	1 (14·3)	21 (34·4)	··	0 (0·0)	21 (38·9)	··
unknown	2 (28·6)	0 (0·0)	··	0 (0·0)	2 (3·7)	··

**Chi* square test;
¶Digits in the parentheses are percentages if not defined·
NA=not applicable

Table 6: Relation between Arbidol and Oseltamivir for prevention of COVID-19 infection in health care workers

Treatment	COVID-19 Infection	Control	OR (95% CI) *	*P**
Oseltamivir, No. (%)	7 (87·5)	61(53·0)	1·00 (Reference)	··
Arbidol, No. (%)	1 (12·5)	54 (47·0)	0·049 (0·003-0·717)	0·0276

* Logistic regression calculations, gender, age, occupation and working place adjusted
No.= Number

Table 7: Relation between two forms of preventive treatment (Oseltamivir or Arbidol) and COVID-19 infection in health care workers

Treatment		COVID-19 Dignoesed No. (%)	Normal No. (%)	OR (95% CI) *	*P**
Oseltamivir	NO	1 (12·5)	55 (47·4)	1·00 (Reference)	··
	YES	7 (87·5)	61 (52·6)	20·446 (1·407-297·143)	0·0271
Arbidol	NO	7 (87·5)	62 (53·4)	1·00 (Reference)	··
	YES	1 (12·5)	54 (46·6)	0·051 (0·004-0·733)	0·0286

* Logistic regression calculations, gender, age, occupation and working place adjusted
No.= Number